IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: KEVY et al.	Attorney Dkt. No.: 1459.008A
Serial No.: 10/765,694	Examiner: SCHUBERG, Laura J.
Filed: January 27, 2004	Group Art Unit: 1657

Title: AUTOLOGOUS COAGULANT PRODUCED FROM ANTICOAGULATED WHOLE BLOOD

To: Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 CFR §1.132

I, Robert J. Mandle, citizen of the United States of America and residing at 7 Muster Court, Lexington, MA 02420, declare that:

1. I have no authorship or association with the above-captioned patent application or its assignee.

2. I am currently an investigator in the Immune Disease Institute/Program in Cellular and Molecular Medicine at Children's Hospital, Harvard Medical School, Boston, Massachusetts, and specialize in assay development and medical device testing. A copy of my Curriculum Vitae is attached herewith. Previously, I completed a post-doctoral fellowship with a research emphasis on purification and characterization of complement proteins from human plasma.

3. I have read the Office Action dated December 15, 2007, wherein the Examiner has rejected claims 1, 2, 7 and 19 of the present application under 35 U.S.C. §103, as obvious in view of McGinnis et al. (U.S. 2004/0120942) published June 24, 2004. I have also read the invention disclosure dated April 21, 2002 and the 132 declaration of Dr. Sherwin V. Kevy. I agree with Dr. Kevy's description and analysis of the state of the art at the time the disclosure was filed for this application. The Office Action states that McGinnis discloses a method for obtaining thrombin from a whole blood preparation without having to first obtain a plasma fraction from the whole blood. According to the Office Action, one of ordinary skill would have

been motivated to use whole blood in the process/device of McGinnis because it would have shortened and simplified the process of obtaining thrombin. Furthermore, the Office Action maintains that one of ordinary skill would have had a reasonable expectation of success because McGinnis teaches that the device that is used for the process is suitable for use with whole blood.

4. The rejected claims are directed to a method for the production of a coagulant (for example, thrombin) from anticoagulated whole blood, the method comprising the steps of obtaining a volume of anticoagulated whole blood from a subject, mixing said anticoagulated whole blood with a precipitating agent, incubating the mixture for a time sufficient to produce a cellular and specific plasma component precipitate and a supernatant, separating the precipitate from the supernatant; and recovering the supernatant wherein said supernatant is used as a coagulant.

5. The Office Action states that McGinnis discloses a method for obtaining thrombin from a whole blood sample without first fractionating the formed elements from the plasma or platelet rich fraction. McGinnis does repeatedly claim a device that can use "whole blood, plasma, or plasma fraction", however, in my opinion, no evidence by example or method claim supports that the device claim could directly produce thrombin from whole blood

6. The McGinnis reference supports the production of thrombin from plasma fractions and does not suggest a method for production using whole blood without first removing cellular elements from the plasma, consistent with the expectation of one skilled in the art, and is further supported by McGinnis in that all method claims and preferred starting material for the invention is cell-free plasma fraction and not whole blood.

7. One of skill in the art at the time of the McGinnis disclosure would have known that precipitation of an anticoagulated whole blood preparation would result in a preparation containing significant levels of cell debris and undesirable cellular proteins not present in a similarly processed plasma preparation. One of skill in the art at this time would have believed that the presence of these proteins and other debris would be likely to degrade or otherwise interfere with the quality of attempted protein isolations, due to the higher chance of contamination in the form of undesired proteins being present in the final sample.

8. At the time the application was filed, the standard of practice for the production of a thrombin preparation from human blood, as outlined by Dr. Kevy, consisted of taking a sample of anticoagulated whole blood and first removing the cells to obtain a plasma fraction. Typically, blood fractionation of this sort involved centrifuging anticoagulated whole blood to separate the blood components according to density, allowing recovery of an essentially cell-free plasma fraction. After centrifugation, the blood is separated into an upper plasma fraction, comprising ~60% of the sample volume, a lower red blood cell fraction comprising ~40%, and a thin interface layer that comprises primarily leukocytes. For preparation of thrombin from plasma, the upper plasma fraction is recovered by aspiration and further processed to obtain the thrombin preparation.

9. As pointed out by Dr. Kevy, as late as 2005, the relevant art, including the examples in McGinnis et al., taught only the use of plasma for the production of human thrombin (See Kumar et al. *Stability of human thrombin produced from 11 ml of plasma using the thrombin processing device.* J Extra Corpor Technol. 37:390-395 2005). Preparation of thrombin from whole blood, without a plasma isolation step, was not viewed in the art as desirable due to the presence of a significant amount of extraneous debris. In my opinion, the invention shows an unexpected result of using whole blood, in that the hemolysis that occurs during preparation of the sample may actually *enhance* the process in terms of reducing the time required for agglomeration and precipitation of inhibitor proteins, compared to using plasma as a starting material. This phenomenon is described in the invention disclosure, on page 4, and also in paragraph [0015] of the specification of the application as originally filed. However, I believe one of skill in the art at the time would have come to the opposite conclusion.

10. In my opinion, until the discovery that is the subject of the current application, the production of thrombin or other plasma proteins from whole blood would first require separation of cells from anticoagulated blood either by centrifugation or by filtration to produce plasma. Further, the activation of the coagulation cascade in the presence of blood cells in order to produce a clinical coagulant would not have been obvious or advisable to one skilled in the art at the time of disclosure.

11. I further declare that all statements of the foregoing Declaration made of my own knowledge are true and that all statements made upon information and belief are believed true

and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the above identified application or any patent issuing thereon.

25 Jan 2010
Date

Robert J. Mandle, Ph.D.